

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number  
WO 03/074019 A1(51) International Patent Classification<sup>7</sup>: A61K 7/48

(21) International Application Number: PCT/JP03/02646

(22) International Filing Date: 6 March 2003 (06.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
2002-061120 6 March 2002 (06.03.2002) JP  
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(JP).(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK,  
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,  
MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,  
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VC, VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG,  
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU,  
SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,  
UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,  
GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR),  
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG)— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG,  
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SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,  
UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,  
GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR),  
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG)— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for the following design-  
ations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,  
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL,  
PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,  
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent  
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

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(54) Title: WHITENING COSMETIC COMPOSITION

(57) Abstract: A preparation for external use on skin which comprises an active ingredient exhibiting superior effects of preventing pigmentation or eliminating pigments formed in the skin, and has a high level of safety, and in particular, a cosmetic composition exhibiting superior so-called whitening effects, are provided. The whitening cosmetic composition comprises a tocopherol alkyl-glycine ester and/or a salt thereof.

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*European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## DESCRIPTION

## WHITENING COSMETIC COMPOSITION

## 5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit pursuant to 35 U.S.C. §119(e) of U.S. Provisional Application No. 60/363,102 filed March 12, 2002, pursuant to 35 U.S.C. §111(b).

## 10 TECHNICAL FIELD

The present invention relates to a preparation for external use on skin and to a whitening cosmetic composition, characterized by comprising a tocopherol alkylglycine ester and/or a salt thereof, as an active ingredient, exhibiting  
15 effects of preventing pigmentation or eliminating formed pigments in the skin.

## BACKGROUND ART

Heretofore, many preparations for external use on skin  
20 have been proposed and have been employed, in order to reduce pigmentation of the skin, such as spots and freckles due to exposure to UV rays, or darkening observed after wounds or burns heal or observed after healing surgical operation wounds.

25 For example, polyphenols are widely known as reducing

decoloration effects of melanin pigments. In particular, hydroquinone is widely employed in the field of clinical medicine in USA. However, hydroquinone is pointed out as being strongly irritating on the skin, and for this reason, it is difficult to employ it as a preparation for external use on skin, having a satisfactory level of safety.

In addition, vitamin C or derivatives thereof such as ascorbyl 2-phosphate or ascorbyl 2-glucoside have been widely employed as pigmentation preventive agents in cosmetic compositions. However, according to our knowledge, the effects of preventing pigmentation of the ascorbic acids described above are weak, and they cannot be believed to be effective in view of many aspects. Furthermore, they exhibit superior effects of preventing pigmentation, but the effects of reducing deposition of the formed pigments may or may not be sufficient.

Tocopherols, also known as vitamin E (such as  $\alpha$ -tocopherol,  $\beta$ -tocopherol,  $\gamma$ -tocopherol, and  $\delta$ -tocopherol), and derivatives thereof such as tocopherol acetate and tocopherol nicotinate, are known to exhibit effects such as antioxidation effects, effects of stabilizing vital membranes, immune activating effects, and effects of accelerating blood circulation, and have heretofore been added to medicines, cosmetics, and the like; however, there has been no reference to their effects of preventing pigmentation or eliminating

formed pigments. As for tocopherols, there is an example of their effect as a remedy for pigmentation by their oral administration (K. Werininghaus et al., Arch Dermatol, 130, 1257, 1997). In addition, there are examples of effects of a specific derivative, tocopherol ferulic acid ester, in inhibiting pigmentation of cultured cells (M. Ichihashi et al., Anticancer Res., 19, 3769, 1999, and the like). However, effects of preventing pigmentation or eliminating formed pigments by dermal application of tocopherols have not been reported.

In addition, in order to avoid difficulty in view of formulation of the oil-soluble tocopherol derivatives described above, water-soluble tocopherol phosphates, amino acid esters, or alkylaminocarbonates have been proposed.

#### DISCLOSURE OF INVENTION

Considering these circumstances, an object of the present invention is to provide a preparation for external use on skin having a high level of safety and comprising an active ingredient exhibiting superior effects of preventing skin pigmentation or eliminating formed pigments in the skin, and in particular, to provide a cosmetic composition exhibiting superior so-called "whitening effects".

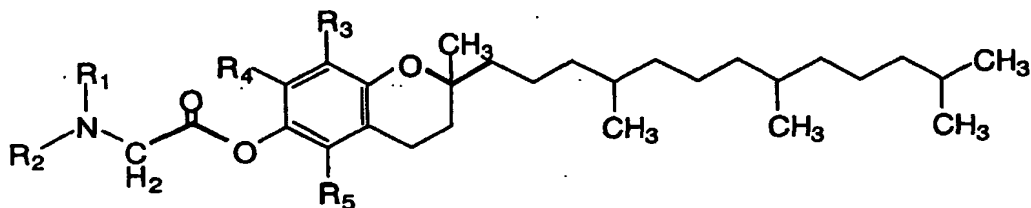
As a result of diligent research in order to achieve this object, the present inventors discovered that tocopherol

alkylglycine esters and salts thereof exhibit strong effects of preventing skin pigmentation and eliminating formed pigments in the skin, thus completing the present invention.

That is, the present invention relates to the features described below.

[1] A whitening cosmetic composition characterized by comprising a tocopherol alkylglycine ester and/or a salt thereof.

[2] The whitening cosmetic composition according to [1] described above, wherein the tocopherol alkylglycine ester is a compound represented by formula (1) described below:



(1)

wherein R<sub>1</sub> and R<sub>2</sub> represent the same or different lower alkyl group or a hydrogen atom; and R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> represent a hydrogen atom or a methyl group; with the proviso that R<sub>1</sub> and R<sub>2</sub> do not represent a hydrogen atom at the same time.

[3] The whitening cosmetic composition according to [1] or [2] described above, wherein the tocopherol alkylglycine ester is at least one compound selected from an  $\alpha$ -tocopherol alkylglycine ester, a  $\gamma$ -tocopherol alkylglycine ester, and a  $\delta$ -tocopherol alkylglycine ester.

[4] The whitening cosmetic composition according to [1]

described above, wherein the tocopherol alkylglycine ester is an  $\alpha$ -tocopherol alkylglycine ester.

[5] The whitening cosmetic composition according to [4] described above, characterized in that the  $\alpha$ -tocopherol alkylglycine ester is a dl- $\alpha$ -tocopherol alkylglycine ester.

[6] The whitening cosmetic composition according to [4] described above, characterized in that the  $\alpha$ -tocopherol alkylglycine ester is a d- $\alpha$ -tocopherol alkylglycine ester.

[7] The whitening cosmetic composition according to [1] or [2] described above, characterized in that the tocopherol alkylglycine ester is a  $\gamma$ -tocopherol alkylglycine ester.

[8] The whitening cosmetic composition according to [7] described above, characterized in that the  $\gamma$ -tocopherol alkylglycine ester is a d- $\gamma$ -tocopherol alkylglycine ester.

[9] The whitening cosmetic composition according to [1] or [2] described above, characterized in that the tocopherol alkylglycine ester is a  $\delta$ -tocopherol alkylglycine ester.

[10] The whitening cosmetic composition according to [9] described above, characterized in that the  $\delta$ -tocopherol alkylglycine ester is a d- $\delta$ -tocopherol alkylglycine ester.

[11] The whitening cosmetic composition according to any one of [1] to [10] described above, characterized in that the tocopherol alkylglycine ester is tocopherol dimethylglycine ester.

[12] The whitening cosmetic composition according to any

one of [1] to [11] described above; characterized in that the salt of a tocopherol alkylglycine ester is a salt of an organic acid or an inorganic acid.

[13] The whitening cosmetic composition according to [12] described above, wherein the salt of a tocopherol alkylglycine ester is hydrochloride.

[14] The whitening cosmetic composition according to any one of [1] to [13] described above, wherein an added amount of the tocopherol alkylglycine ester and/or the salt thereof ranges from 0.1 to 10% by mass.

[15] A method for preventing or eliminating pigmentation of the skin, wherein a tocopherol alkylglycine ester and/or a salt thereof is employed.

[16] Use of a tocopherol alkylglycine ester and/or a salt thereof for preventing or eliminating pigmentation of the skin.

[17] Use of a tocopherol alkylglycine ester and/or a salt thereof for preparation of a pharmaceutical agent for use in preventing or eliminating pigmentation of the skin.

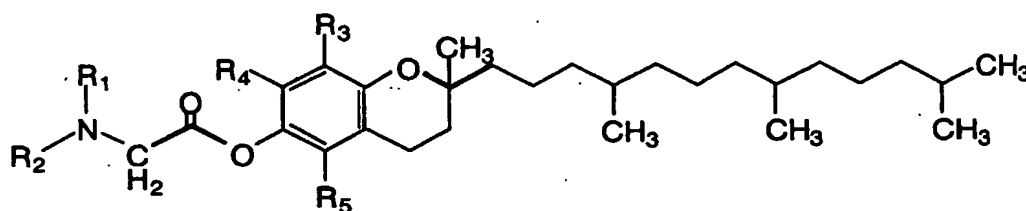
#### BEST MODE FOR CARRYING OUT THE INVENTION

First, a tocopherol alkylglycine ester and a salt thereof which are the ingredients employed in the present invention are described.

A tocopherol alkylglycine ester employed in the present



invention is employed as an active ingredient having effects of preventing pigmentation or eliminating formed pigments in the skin, and is a compound represented by, for example, a formula (1) described below:



(1)

wherein  $R_1$  and  $R_2$  represent the same or different lower alkyl group or a hydrogen atom; and  $R_3$ ,  $R_4$ , and  $R_5$  represent a hydrogen atom or a methyl group; with the proviso that  $R_1$  and  $R_2$  do not represent a hydrogen atom at the same time.

The term "lower alkyl group" described in the definition of  $R_1$  and  $R_2$  means a straight-chain or branched alkyl group having 1 to 6 carbon atoms. As examples thereof, mention may be made of methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl, n-hexyl, and the like. The most preferable group among these is a methyl group.

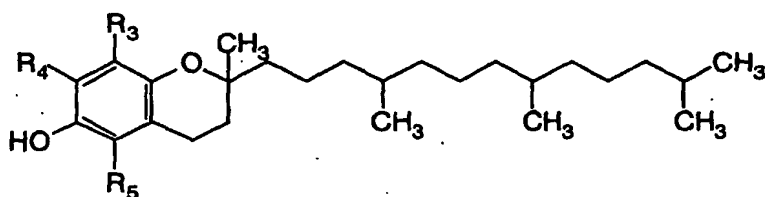
As a salt of the compound of the present invention, salts are not particularly restricted, so long as they are salts of an organic acid or an inorganic acid. As preferable examples thereof, mention may be made of a hydrohalogenic acid salt, an organic acid salt, and the like. Among these, hydrochloride is preferable since it is advantageous in that the solubility

in water increases and handling is facilitated due to its powdered form.

The tocopherol derivatives represented by the formula (1) described above have an asymmetric carbon at the 2-position of the chroman ring. For this reason, there are stereomers such as d-form, l-form, and dl-form. It should be understood that the present invention includes all the isomers described above.

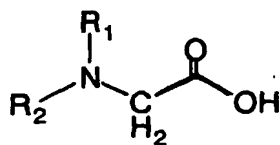
The compounds of the present invention may be produced by conventional production methods, and an example thereof is described in the following.

The compounds can be easily produced by performing an esterification reaction between a tocopherol represented by the formula (2) described below:



(2)

wherein  $R_3$ ,  $R_4$ , and  $R_5$  represent a hydrogen atom or a methyl group,  
and any one of an alkylglycine represented by the formula (3) described below:



(3)

wherein  $R_1$  and  $R_2$  represent an identical or different lower alkyl group or a hydrogen atom; with the proviso that  $R_1$  and  $R_2$  do not represent a hydrogen atom at the same time,  
5 a reactive acid derivative thereof, and a hydrohalogenic acid salt thereof, in a conventional manner.

In the case of directly performing the esterification using a free alkylglycine, usually, the reaction is preferably performed in the presence of an active esterification reagent  
10 such as dicyclohexylcarbodiimide or N,N-disuccinimide oxalate. The solvent in the reaction is most preferably pyridine.

In addition, in a reaction with a reactive acid derivative, a reaction employing an acyl halide, and in particular, an acyl chloride is preferable.

15 In the case of producing a salt of a tocopherol alkylglycine ester, the hydrohalogenic acid salt may be produced by once producing an ester form, and subsequently adding an acid thereto according to a conventional method, thus forming a salt, or alternatively, may be produced by  
20 previously employing a salt of an alkylglycine as a starting material.

The present invention relates to a whitening cosmetic composition comprising a tocopherol alkylglycine ester and a

salt thereof.

The whitening cosmetic composition can be produced by adding 0.1 to 10% by mass and preferably 0.5 to 2% by mass of a tocopherol alkylglycine ester and/or a salt thereof to an alcohol such as ethanol or propylene glycol; preservatives  
5 such as methyl parahydroxybenzoate, ethyl parahydroxybenzoate, butyl parahydroxybenzoate, or propyl parahydroxybenzoate; purified water; and the like.

Examples of whitening cosmetic compositions include, for  
10 example, skin milk, skin cream, foundation cream, cream for massaging, cleansing cream, lotion, pack, ointment, bath preparation, body soap, and the like. The kinds thereof are not restricted, so long as they come into contact with skin during use. They may be in the form of gel. In addition, the  
15 user may be any user irrespective of sex or age.

In addition, in the whitening cosmetic compositions of the present invention, ingredients other than those described above, which are commonly employed in whitening cosmetic compositions, can be added within a range which does not  
20 impair the effects of the present invention.

#### EXAMPLES

In the following, the present invention is described in detail by referring to Examples. It should be understood that  
25 the present invention is not restricted to these Examples. In

the Examples, the added amount is based on % by mass.

#### Example of Synthesis

To a solution of 59.1 g of dicyclohexylcarbodiimide and  
5 40.0 g of N,N-dimethylglycine hydrochloride dissolved in 320 g  
of pyridine, a solution of 60.0 g of dl- $\alpha$ -tocopherol dissolved  
in 240 g of pyridine was added. The mixture was allowed to  
react for 8 hours while stirring at room temperature, and  
pyridine was distilled out. 2000 ml of water and 1000 ml of  
10 ethyl acetate were added to the residue, and about 40 g of  
sodium carbonate was added thereto to adjust the pH to between  
7 and 8. The ethyl acetate phase was separated. Extraction  
from the water phase was carried out three time using 200 ml  
of ethyl acetate each time. The ethyl acetate phase which was  
15 separated and the ethyl acetate phases used for extraction  
were combined, and the ethyl acetate was distilled off. Ethyl  
acetate was added to the residue, the mixture was dried over  
anhydrous sodium sulfate, and solid substances were filtered  
out. The concentration of dl- $\alpha$ -tocopherol dimethylglycine  
20 ester in the filtrate was adjusted to between 7 to 8%. 20%  
hydrochloric acid in dioxane was added thereto for  
neutralization in an amount such that the molar amount of the  
hydrochloric acid is 1.5 times of that of the dl- $\alpha$ -tocopherol  
dimethylglycine ester. Solid substance obtained was collected  
25 by filtration, and recrystallized in methanol/acetone solvent

to yield 49.2 g of dl- $\alpha$ -tocopherol dimethylglycine ester hydrochloride.

#### Example 1

5

#### Lotion 1

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to  
10 ingredient 5) with stirring, thus producing Lotion 1.

1) dl- $\alpha$ -tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

#### Lotion 2

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described  
15 below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 2.

1) d- $\alpha$ -tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00

4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

## Lotion 3

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 3.

1) d- $\gamma$ -tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

## Lotion 4

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 4.

1) d- $\delta$ -tocopherol dimethylglycine ester hydrochloride	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

## Lotion 5 (Comparative control)

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to

5 ingredient 5) with stirring, thus producing Lotion 5.

1) Sodium ascorbyl 2-phosphate	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

## Lotion 6 (Negative control)

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described

10 below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 6.

1) Purified water	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	87.8

All lotions described above were uniformly dissolved and exhibited good stability over time.



## Lotion 7

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 7.

1) dl- $\alpha$ -tocopherol dimethylglycine ester hydrochloride	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

## Lotion 8

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 8.

1) d- $\alpha$ -tocopherol dimethylglycine ester hydrochloride	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

## Lotion 9

Ingredients 1) to 4) were uniformly dispersed and

dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 9.

1) d- $\gamma$ -tocopherol dimethylglycine ester hydrochloride	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

#### 5 Lotion 10

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 10.

1) d- $\delta$ -tocopherol dimethylglycine ester hydrochloride	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

10

#### Lotion 11 (Comparative control)

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to

15 ingredient 5) with stirring, thus producing Lotion 11.

1) Sodium ascorbyl 2-phosphate	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

#### Lotion 12 (Negative control)

Ingredients 1) to 4) were uniformly dispersed and dissolved so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 5) with stirring, thus producing Lotion 12.

1) Purified water	0.10
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl parahydroxybenzoate	0.20
5) Purified water	89.7

All lotions described above were uniformly dissolved and exhibited good stability over time.

10

#### Example 3

##### Gel composition 1

Ingredient 1) was uniformly dispersed in ingredient 2) so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 3)

15

with stirring, thus producing the desired gel composition 1.

- |   |    |
|---|----|
| 1) dl- $\alpha$ -tocopherol dimethylglycine ester hydrochloride | 10 |
| 2) Glycerol   | 20 |
| 3) Octyldodecyl myristate                                       | 70 |

#### Gel composition 2

Ingredient 1) was uniformly dispersed in ingredient 2) so  
5 as to obtain the final concentrations described below, and  
subsequently the resulting mixture was added to ingredient 3)  
with stirring, thus producing the desired gel composition 2.

- |  |    |
|--|----|
| 1) d- $\alpha$ -tocopherol dimethylglycine ester hydrochloride | 10 |
| 2) Glycerol  | 20 |
| 3) Octyldodecyl myristate                                      | 70 |

#### Gel composition 3

10 Ingredient 1) was uniformly dispersed in ingredient 2) so  
as to obtain the final concentrations described below, and  
subsequently the resulting mixture was added to ingredient 3)  
with stirring, thus producing the desired gel composition 3.

- |  |    |
|--|----|
| 1) d- $\gamma$ -tocopherol dimethylglycine ester hydrochloride | 10 |
| 2) Glycerol  | 20 |
| 3) Octyldodecyl myristate                                      | 70 |

#### 15 Gel composition 4

Ingredient 1) was uniformly dispersed in ingredient 2) so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 3) with stirring, thus producing the desired gel composition 4.

1) d- $\delta$ -tocopherol dimethylglycine ester hydrochloride	10
2) Glycerol	20
3) Octyldodecyl myristate	70

5

Gel composition 5 (Comparative control)

Ingredient 1) was uniformly dispersed in ingredient 2) so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 3) with stirring, thus producing the desired gel composition 5.

10

1) Sodium ascorbyl 2-phosphate	10
2) Glycerol	20
3) Octyldodecyl myristate	70

Gel composition 6 (Negative control)

Ingredient 1) was uniformly dispersed in ingredient 2) so as to obtain the final concentrations described below, and subsequently the resulting mixture was added to ingredient 3) with stirring, thus producing the desired gel composition 6.

15

1) Purified water	10
2) Glycerol	20
3). Octyldodecyl myristate	70

All gel compositions described above were uniformly dissolved, and exhibited good stability over time.

5 Example 4

Effects of preventing pigmentation

Hair on the entire surface of the back of each of 50 male Wiser Maple guinea pigs (WM, SPF), 7 weeks old, was cut by means of electric hair clippers (0.05 mm blade), and was  
10 subsequently shaved by means of an electric shaver, followed by covering with an adhesive stretch bandage (SILKYTEX, covered on the outside thereof with an aluminum foil) wherein 6 holes of 1.5 cm × 1.5 cm had been formed.

Each product of the Lotions 1 to 12 and the Gel  
15 compositions 1 to 6, prepared in Examples 1 to 3, in an amount of 0.05 ml, was successively applied to 10 holes described above.

Four hours after the application, the application part was cleaned with absorbent cotton which contained water,  
20 followed by drying. Subsequently, the animal was held by a retainer, followed by exposure of UV rays having medium wavelength (UVB) with 300 mJ/cm<sup>2</sup> to each part from a distance of approximately 10 cm by means of a UV exposure apparatus (Shinano Co., Ltd., Toshiba FL40S/E30 model fluorescent lamp,  
25 equipped with six SE lamps).

After the exposure, 0.05 ml of each of the same Lotions 1 to 12 and Gel compositions 1 to 6 as described above was again applied to the corresponding part.

The operation described above was repeated for 3 days.

5 Fourteen days after the final exposure, the strength of pigmentation was evaluated by evaluation points according to the evaluation criteria described in the following. Furthermore, the lightness of the skin at 5 spots in total, that is, the four corners and the center part of each of the  
10 applied and exposed parts was measured by means of a color-difference meter (Minolta Co., Ltd., CR-20).

The effects of preventing pigmentation of each of the products were determined by the average value of the evaluation points (10 pieces of data per product) and the  
15 average value of the lightness (50 pieces of data per product).

#### Evaluation criteria of pigmentation

No pigmentation is observed	evaluation point 0
Very slight pigmentation is observed	evaluation point 1
Slight pigmentation is observed	evaluation point 2
Fair degree of pigmentation is observed	evaluation point 3
Strong pigmentation is observed	evaluation point 4

## Results (average value)

Product	Evaluation point	Lightness
Lotion 1	0.8	63.0
Lotion 2	0.7	63.1
Lotion 3	0.6	62.8
Lotion 4	0.5	64.0
Lotion 5	2.1	61.8
Lotion 6	3.0	59.5
Lotion 7	2.0	61.7
Lotion 8	2.0	60.7
Lotion 9	1.5	62.0
Lotion 10	1.7	62.0
Lotion 11	3.0	59.9
Lotion 12	3.0	60.1
Gel composition 1	0.4	63.8
Gel composition 2	0.4	62.9
Gel composition 3	0.4	63.1
Gel composition 4	0.4	63.0
Gel composition 5	1.2	62.1
Gel composition 6	3.0	59.9

As is apparent from the results described above, in each  
5 of the Lotions 1 to 4 and 7 to 10, and the Gel compositions 1  
to 4, according to the present invention, superior effects of  
preventing pigmentation were observed.



## Example 5

## Effects of eliminating pigmentation

Hair on the entire surface of the back of each of 50 male  
5 Wiser Maple guinea pigs (WM, SPF), 6 weeks old, was cut by  
means of electric hair clippers (0.05 mm blade), and was  
subsequently shaved by means of an electric shaver, followed  
by covering with an adhesive stretch bandage (SILKYTEX,  
covered the outside thereof with an aluminum foil) wherein 6  
10 holes of 1.5 cm × 1.5 cm had been formed. Subsequently, the  
animal was held by a retainer, followed by exposure of UV rays  
having medium wavelength (UVB) of 750 mJ/cm<sup>2</sup> to each part from  
a distance of approximately 10 cm by means of a UV exposure  
apparatus (Shinano Co., Ltd., Toshiba FL40S/E30 model  
15 fluorescent lamp, equipped with six SE lamps).

From 4 days after the exposure to 28 days, each product  
of the Lotions 1 to 12 and the Gel compositions 1 to 6,  
prepared in Examples 1 to 3, in an amount of 0.05 ml, was  
successively applied to 10 holes described above, twice a day,  
20 that is, in the morning and in the evening.

Twenty-eight days after the exposure, the strength of  
pigmentation was evaluated by evaluation points according to  
the same evaluation criteria as described in the Example. The  
effects of preventing pigmentation were evaluated by the  
25 average value obtained from the evaluation points (10 data per

product).

Results (average value)

Product	Evaluation point
Lotion 1	2.2
Lotion 2	2.2
Lotion 3	2.0
Lotion 4	2.0
Lotion 5	3.3
Lotion 6	3.5
Lotion 7	3.0
Lotion 8	3.0
Lotion 9	3.0
Lotion 10	3.0
Lotion 11	3.5
Lotion 12	3.8
Gel composition 1	2.2
Gel composition 2	2.1
Gel composition 3	2.0
Gel composition 4	1.9
Gel composition 5	2.9
Gel composition 6	3.5

As is apparent from the results described above, even in each of the Lotions (1 to 4 and 7 to 10) and Gel compositions

(1 to 4) according to the present invention, superior effects of eliminating pigmentation were observed.

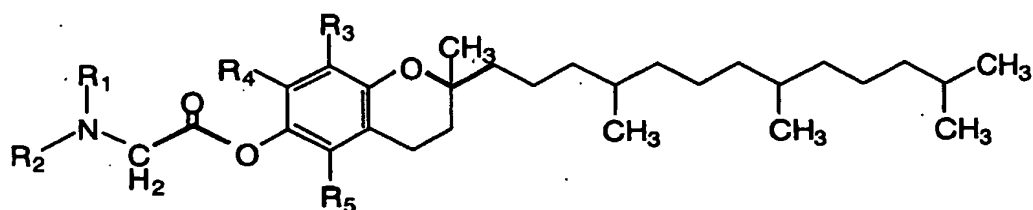
#### INDUSTRIAL APPLICABILITY

5       The whitening cosmetic compositions of the present invention have a high level of safety, and exhibit superior effects of preventing pigmentation or eliminating formed pigments in the skin. For these reasons, they are useful as cosmetic compositions exhibiting superior so-called whitening  
10 effects.

## CLAIMS

1. A whitening cosmetic composition characterized by comprising a tocopherol alkylglycine ester and/or a salt thereof.

2. The whitening cosmetic composition according to Claim 1, wherein the tocopherol alkylglycine ester is a compound represented by a formula (1) described below:



(1)

wherein R<sub>1</sub> and R<sub>2</sub> represent the same or different lower alkyl group or a hydrogen atom; and R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> represent a hydrogen atom or a methyl group; with the proviso that R<sub>1</sub> and R<sub>2</sub> do not represent a hydrogen atom at the same time.

3. The whitening cosmetic composition according to Claim 1, wherein the tocopherol alkylglycine ester is at least one compound selected from an  $\alpha$ -tocopherol alkylglycine ester, a  $\gamma$ -tocopherol alkylglycine ester, and a  $\delta$ -tocopherol alkylglycine ester.

4. The whitening cosmetic composition according to Claim 1,

wherein the tocopherol alkylglycine ester is an  $\alpha$ -tocopherol alkylglycine ester.

5. The whitening cosmetic composition according to Claim 4,  
5 characterized in that the  $\alpha$ -tocopherol alkylglycine ester is a  
dl- $\alpha$ -tocopherol alkylglycine ester.

6. The whitening cosmetic composition according to Claim 4,  
characterized in that the  $\alpha$ -tocopherol alkylglycine ester is a  
10 d- $\alpha$ -tocopherol alkylglycine ester.

7. The whitening cosmetic composition according to Claim 1,  
characterized in that the tocopherol alkylglycine ester is a  
 $\gamma$ -tocopherol alkylglycine ester.

15

8. The whitening cosmetic composition according to Claim 7,  
characterized in that the  $\gamma$ -tocopherol alkylglycine ester is a  
d- $\gamma$ -tocopherol alkylglycine ester.

20 9. The whitening cosmetic composition according to Claim 1,  
characterized in that the tocopherol alkylglycine ester is a  
 $\delta$ -tocopherol alkylglycine ester.

10. The whitening cosmetic composition according to Claim 9,  
25 characterized in that the  $\delta$ -tocopherol alkylglycine ester is a

d- $\delta$ -tocopherol alkylglycine ester.

11. The whitening cosmetic composition according to Claim 1,  
characterized in that the tocopherol alkylglycine ester is  
5 tocopherol dimethylglycine ester.

12. The whitening cosmetic composition according to Claim 1,  
characterized in that the salt of a tocopherol alkylglycine  
ester is a salt of an organic acid or an inorganic acid.

10

13. The whitening cosmetic composition according to Claim 12,  
wherein the salt of a tocopherol alkylglycine ester is  
hydrochloride.

15 14. The whitening cosmetic composition according to Claim 1,  
wherein an added amount of the tocopherol alkylglycine ester  
and/or the salt thereof ranges from 0.1 to 10% by mass.

20 15. A method for preventing or eliminating pigmentation of  
the skin, wherein a tocopherol alkylglycine ester and/or a  
salt thereof is employed.

25 16. Use of a tocopherol alkylglycine ester and/or a salt  
thereof for preventing or eliminating pigmentation of the  
skin.

17. Use of a tocopherol alkylglycine ester and/or a salt thereof for preparation of a pharmaceutical agent for use in preventing or eliminating pigmentation of the skin.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/02646

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, PAJ, EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 037290 A (SHOWA DENKO K.K.) 8 May 2003 (2003-05-08) claim 38; examples 1,3,5,7,9,11,12,15,16,21,23,25,26,29,31,33 ,34,37	1-5,7, 11-14
X	US 2 988 553 A (HANS-WALTER VOIGTLANDER ET AL) 13 June 1961 (1961-06-13) column 1, line 10-16; claims 1-5,7; examples 3,5-7	1-5, 11-13
X	PATENT ABSTRACTS OF JAPAN vol. 014, no. 397 (C-0752), 28 August 1990 (1990-08-28) & JP 02 149577 A (EISAI CO LTD), 8 June 1990 (1990-06-08) abstract	1-5,12, 13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

8 August 2003

Date of mailing of the international search report

21/08/2003

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## INTERNATIONAL SEARCH REPORT

Application No

PCT/JP 03/02646

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIRO TAKATA ET AL: "PRODRUGS OF VITAMIN E.1" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 84, no. 1, 1995, pages 96-100, XP002092803 ISSN: 0022-3549 page 98, right-hand column, last paragraph page 99, left-hand column, paragraphs 2,3 ---	1-4,6, 11-13
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AOKI, YUZURU ET AL: "Skin cosmetics containing vitamin E derivatives and Citrus junos extracts" retrieved from STN Database accession no. 134:256613 CA XP002250037 abstract & JP 2001 081022 A (KANEBO, LTD., JAPAN) 27 March 2001 (2001-03-27) ---	15-17
X	US 5 932 612 A (GORDON BENJAMIN D ET AL) 3 August 1999 (1999-08-03) column 1, line 44-60; claim 1 ---	15-17
X	WO 98 51679 A (LVMH RECH ;BONTE FREDERIC (FR); SAUNOIS ALEX (FR)) 19 November 1998 (1998-11-19) claims 1,15,16 -----	15-17

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Information on patent family members

International Application No

PCT/JP 03/02646

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